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STITES & HARBISON PLLC
401 COMMERCE STREET
SUITE 800
NASHVILLE, TN 37219

EXAMINER	
PAK, YONG D	
ART UNIT	**PAPER NUMBER**
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/924,082	MARNETT ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6,7,9-43,49-59,61 and 62* is/are pending in the application.

4a) Of the above claim(s) *22-43 and 49-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4, 6-7, 9-21, 55-59 and 61-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on December 4, 2007, amending claims 4, 6, 13, and 56 and canceling claim 8, has been entered.

Claims 4, 6-7, 9-43, 49-59 and 61-62 are pending. Claims 22-43 and 49-54 are withdrawn. Claims 4, 6-7, 9-21, 55-59 and 61-62 are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on December 4, 2007, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claim 6 is objected to because of the following informalities:

Claim 6 recites the phrases "living mammalian". It appears that applicants have meant to recite "living mammal". Amending the claim to recite "living mammal" would overcome the rejection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the phrase "relating the amount of the PGH_2-EA metabolite quantified in the sample to the activity of the COX-2 enzyme in the subject from which the sample was taken". The metes and bounds of the phrase in the context of the claim are not clear. This is because it is not clear to the Examiner how one of skill in the art "relates" the amount of the PGH_2-EA metabolite to the activity of the COX-2 enzyme in the subject, and thereby measuring COX-2 activity in a "living subject". Therefore, the method lacks essential step(s).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that the specification has not been considered. Examiner respectfully disagrees. A perusal of the specification did not provide the Examiner with how one of skill in the art "relates" the amount of the PGH_2-EA metabolite to the activity of the COX-2 enzyme in the subject, and thereby measuring COX-2 activity in a "living subject". Examples 1-7 of the speciation only describes measuring COX-2 activity in a sample taken from a subject. However, if applicants believe that the Examiner is in error, applicants are urged to provide the relevant section of the specification and clarify the record.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al.

Claim 4 is drawn to a method of measuring activity of COX-2 by obtaining a sample from a living mammalian subject, quantifying an amount of PGH_2-EA metabolites and relating the amount of the metabolites to the activity of the COX-2 in a subject.

Yu et al. (Reference BN: PTO-1449) teaches a method of detecting/measuring COX-2 in a sample derived from a mammalian cell, which is a "living mammalian subject", by detecting/measuring a PGH2-EA metabolites (Figures 2-6 and pages 21182). Arachidonyl ethanolamide (AEA), a precursor for PGH_2-EA metabolites is not a substrate for COX-1 and therefore, the method of Yu et al. only selectively detects COX-2 activity (page 21182, right column, page 21183, right column, page 21184, right column and page 21186, left column). The method of Yu et al. "relates the amount of PGH_2-EA metabolites to the activity of the COX-2 enzyme in the subject", since detection and quantification of PGH_2-EA metabolites is indicative of COX-2 activity. Therefore, the teachings of Yu et al. anticipate claim 4.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that there is a problem and confusion in associating a “sample derived from a mammalian cell” as a “living subject”. Examiner respectfully disagrees. It appears that applicants have misinterpreted Examiner's interpretation of a "living subject". A "mammalian cell" is being equated to a living subject", not a "sample” as being a “living subject".

Applicants argue that the present claims indicate that the activity of a COX-2 enzyme is measured in a mammalian subject, which is outside the scope of the cited reference. Examiner respectfully disagrees. As discussed previously, the claims do not recite a limitation of directly detecting/measuring COX-2 enzyme activity in a mammalian subject. Rather, the claims are drawn to a method of measuring activity of COX-2 by detecting/measuring PGH_2-EA metabolites. Yu et al. does teach a method of detecting/measuring activity of COX-2 by detecting PGH_2-EA metabolites (Figures 2-6 and page 21182, right column, page 21183, right column, page 21184, right column and page 21186, left column). Since Yu et al. teaches that arachidonyl ethanolamide (AEA), a precursor for PGH_2-EA metabolites is not a substrate for COX-1, presence and amount of PGH_2-EA metabolites “relates” to the activity of the COX-2 enzyme in a mammalian living subject.

Applicants on page 17, 1st paragraph argue that there is "no disclosure or even a suggestion of the claimed subjects". However, applicants do not state what disclosure or suggestion of the claimed subjects is lacking in the cited reference. Therefore, applicants' argument is moot.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6-7, 9-21 and 55-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al. in view of Tsujii et al.

Claims 6-7, 9-21 and 55-62 are drawn to a method of obtaining a sample from a living mammalian subject, such as urine, detecting/measuring an amount of PGH_2-EA metabolites, relating the amount measure to the activity of the COX-2 enzyme and/or

relating the amount of the metabolites to a disease state or progression of a disease state, such as cancer/tumor, by comparing the activity of the COX-2 enzyme in the subject with a standard value of a previously detected/measured amount, or further generating a standard curve.

The reference of Yu et al. as it applies to claim 4 teaches a method of detecting/measuring COX-2 in a sample by detecting/measuring a PGH2-EA metabolites (Figures 2-6 and pages 21182), as discussed above. Yu et al. also teaches generating a standard value and curve for determining COX-2 activity (Figure 1 and Table 1) and detecting/measuring COX-2 activity by detecting PGH2-EA metabolites via a mass chromatogram (Figures 3-5) and immunoassays (Figure 2 and Figure 6).

The difference between the reference of Yu et al. and the instant invention is that the reference of Yu et al. does not teach a step of relating the amount of the metabolites to a disease state or progression of a disease state, such as cancer/tumor, or by obtaining an urine sample from a subject by comparing the activity of the COX-2 enzyme in the subject with a standard value of a previously detected/measured amount.

However, it is well established and known in the art that COX-2 expression is increased in cancerous cells, such as in colon cancer cells, as disclosed by Taketo et al. (reference BK: form PTO-1449). With this knowledge in hand, one having ordinary skill in the art would have concluded to apply the method of Yu et al. to relate the amount of PGH2-EA metabolites and thereby COX-2 activity to disease state or progression of a disease state, such as colon cancer, by obtaining a sample from a

subject, such as an urine or blood sample, and by comparing the activity of the COX-2 enzyme in the subject with a standard value of a previously detected/measured amount.

Therefore, combining the teachings of Yu et al. and Taketo et al., it would have been obvious to one having ordinary skill in the art to apply the method of Yu et al. in following the progression of colon cancer or to monitor colon cancer in a subject. One of ordinary skill in the art would have been motivated to combine the references in order to follow the progression or monitor colon cancer in a subject. One of ordinary skill in the art would have had a reasonable expectation of success since Yu et al. successfully teaches selective detection/measurement of COX-2 activity in a sample and Taketo et al. teaches that COX-2 expression and thereby activity of COX-2 is increased in colon cancer cells in subjects.

Therefore, the above references render claims 6-7, 9-21 and 55-62 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the rejection should be withdrawn because of the reliance on the improper “mammalian cell/living cell” interpretation as discussed above. Examiner respectfully disagrees. A "mammalian cell" is a “living subject”.

Applicants also point out that Yu et al. grow cultured cells and then induce COX-2 and then determine if the cultured cells metabolize COX-2. It is not clear what applicants are arguing.

Applicants also argue that the office action improperly states that the Yu et al. disclosure "generates a standard value or curve" and that Figure 1 of Yu et al. shows AA and AEA oxygen consumption. Examiner respectfully disagrees. Yu et al. on Figure 1 discloses the standard value of the COX-2 activity. Table 1 discloses the k_m of COX-2 using 2-200uM of AA or AEA, which involves generating a standard curve.

Applicants also argue use of improper hindsight reasoning. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, it should be noted that the knowledge of selective detection/measurement of COX-2 activity in a sample and increased expression of COX-2 activity in cancerous cells were well known and within the level of one having ordinary skill in the art at the time the invention was made.

Applicants also argue that Yu et al. fail to disclose or suggest the downstream metabolites of the present invention and the significance of their presence and quantification. The claims are not drawn to a method of detecting/measuring all the metabolites recited in claims 7 and16. Further, Yu et al. discloses measuring/detecting PGE_2-EA.

Hence the rejection is maintained.

Conclusion

None of the claims are in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652